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Alvotech & Membrane Technology

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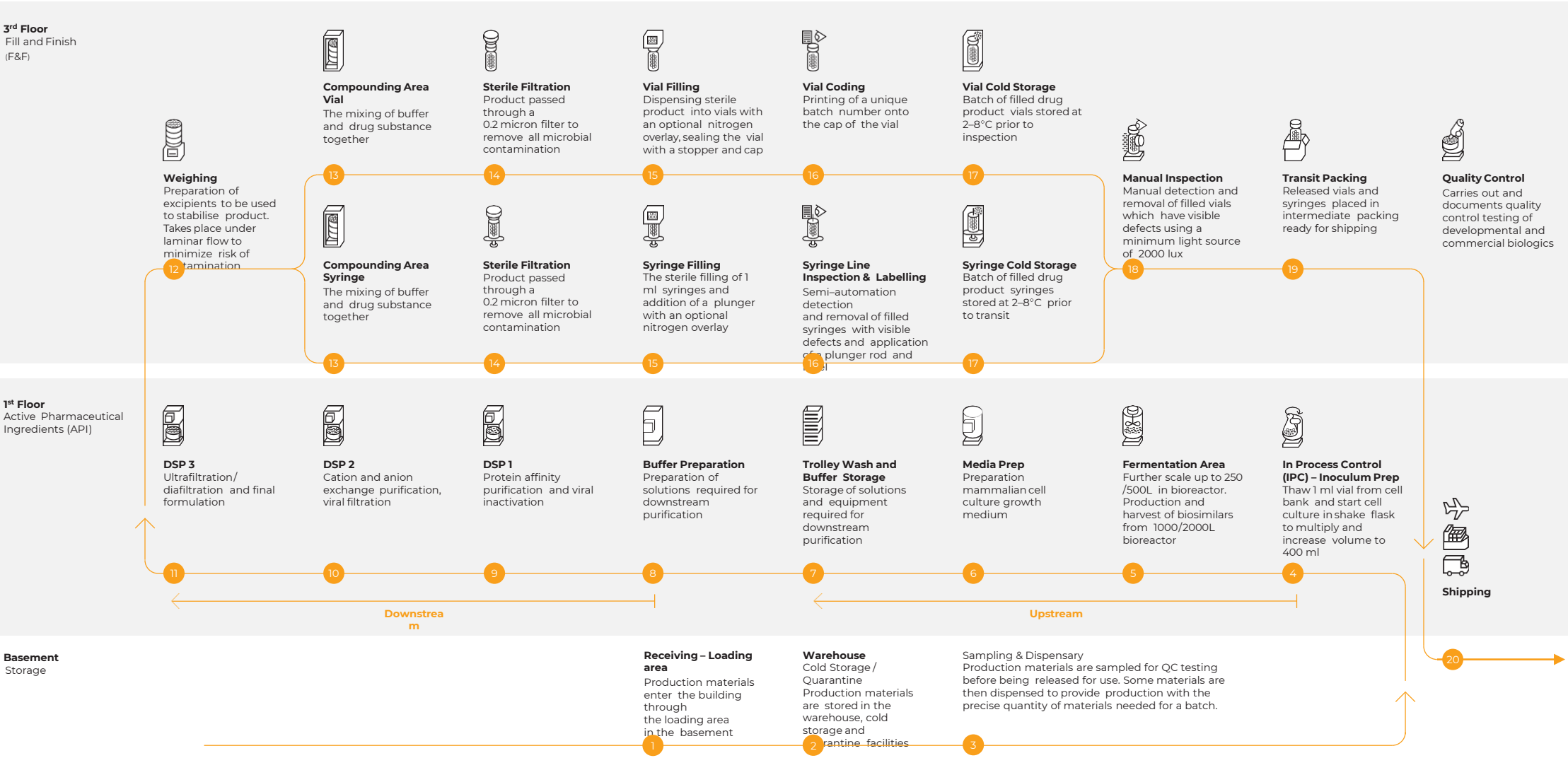
CONTENT OVERVIEW

PRODUCTION FLOW CHART



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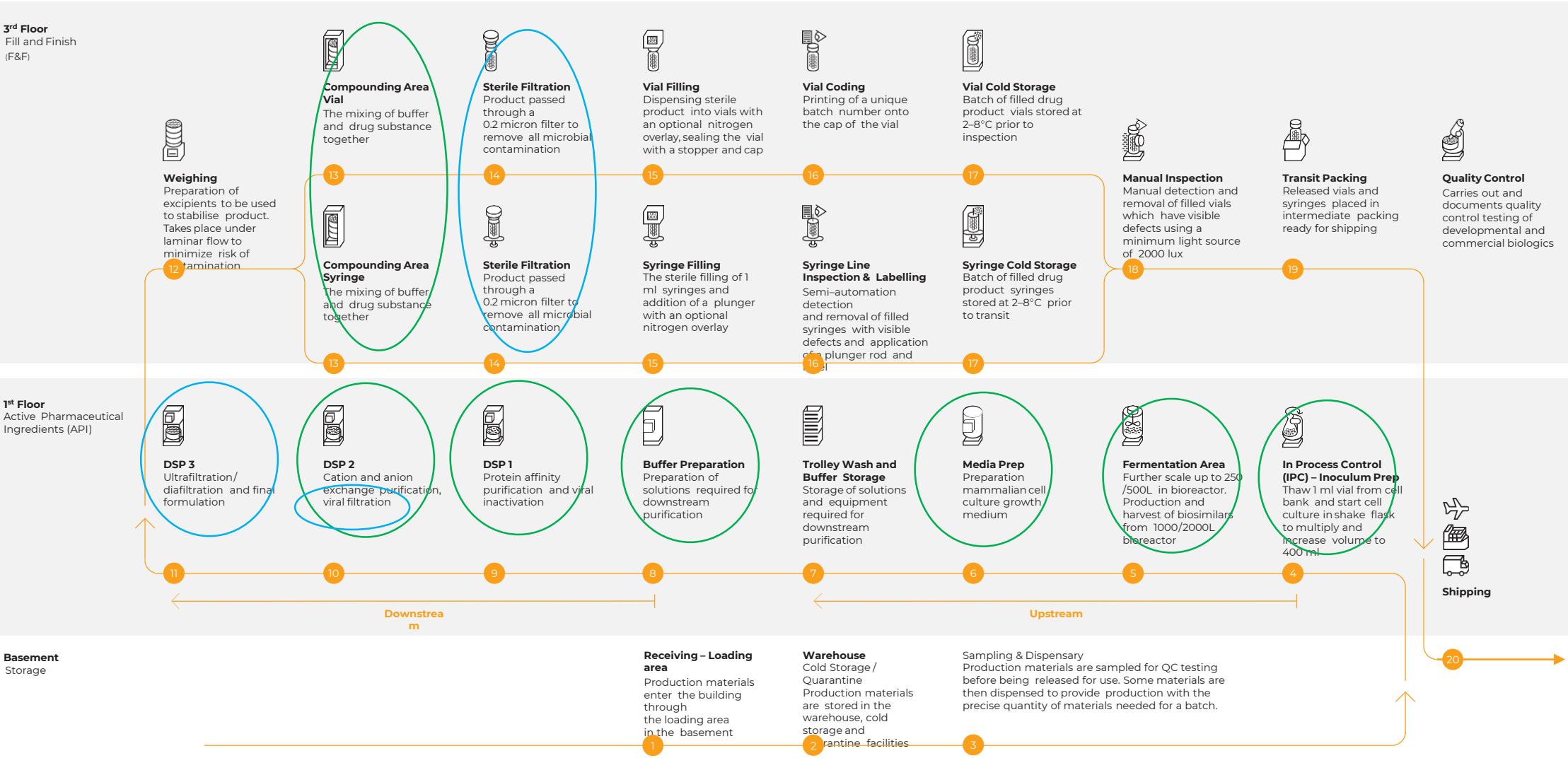
PRODUCTION FLOW CHART



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Biotech characteristics

- Large volumes of purified water used
- Delicate macromolecules sensitive to temperature and environment
- Produced by biological processes sensitive to contaminants
- Products intended for injection – sterility essential

Membrane technology and water purification

- Pharmaceutical regulations define several grades of purified water, the most commonly used in industry are Purified Water (PW) and Water for Injection (WFI).
- In basic terms, PW is required for non-sterile products while for sterile products WFI is used.
- Traditional water purification included filtration, followed by distillation
- Purified Water has for decades been produced by „cold“ techniques
- Filtration and ion exchange deionisation.
- Ion exchange with resins that needed regeneration has now been replaced with electrodeionisation (MT) which is can be operated continuously
- Filtration has been replaced with reverse osmosis – again membrane technology

Membrane technology and water purification

- WFI was required to be prepared by distillation
- Upon review around 2000, membrane technology was found to lack robustness for microbiological quality. Concerns included microbial fouling (biofilms) on membranes, and potential membrane integrity failures.
- In 2010-2011 further review led to an acceptance of non-distillation techniques and since 2017 WFI can be produced using membrane technologies.
- Typical process:
  - Particle filtering
  - Water softening (not needed in Iceland...)
  - Chlorine removal (not needed in Iceland...)
  - Reverse osmosis
  - Electrodeionisation
  - Ultrafiltration

Product purification

- Traditional small molecule pharmaceutical active ingredients
  - Prepared by synthesis or from natural sources
  - Purified by “traditional” methods:
  - Crystallisation, distillation, phase transfers/extraction etc.
- Biotechnology macromolecules
  - Prepared using biological processes
  - Typically in solution throughout - not isolated as pure substances

Membrane technology and product purification

- Non-membrane purification techniques include preparative chromatography
  - Size-exclusion, ion exchange or ligand binding
- Product purification steps where membrane filtration is used:
  - Microfiltration filtration for harvest – cells retained while product passes
  - Nanofiltration to retain potential viruses while allowing product to pass
  - Concentration and buffer exchange: Ultrafiltration/diafiltration using tangential flow
    - Dilute solution of product is circulated over ultrafiltration membrane to concentrate product and remove smaller solutes in permeate. A suitably formulated product solution is added containing any desired solubilizing or stabilizing ingredients.

Membrane technology advantages

- Cold processes – less energy use
- Cold processes – allows use on sensitive molecules
- Steady state or continuous processes – less process variability

Thank you!

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